Columbia University Epidemiology Studies

The agency is obligated to review and address peer review comments in support of regulatory decisions. The following is a list of key issues about the epidemiological studies carried out by researchers at Columbia University that were raised in peer review comments. These issues require EPA to have access to the raw data for additional analyses by the agency.

1) **Further analysis of other chemical exposures (*e.g.,* lead, PAHs, other pesticides) to address, if possible, their impact or contribution as modulating factors on the measured outcomes**

- **2012 SAP --** "it should be noted that it cannot be stated that chlorpyrifos is the sole contributor to the observed outcomes."
  - Multi-variable models adjusted for known confounding variables; not all variables confounding variables; always unmeasured confounding but available evidence within and without CCCEH suggest major ND risk factors accounted for in analyses
  - Proportional risk analysis – what part CPF and Pb – not possible- both play a role
  - Mixtures – not possible, need larger sample size, need more methodological work
  - Resolved: PAH, other Ops, other SES accounted for or not strong risk factors
- **2012 SAP --** "In an earlier examination of the same cohort, Perera *et al.*(2009) reported an association between a decrease in full-scale IQ and verbal IQ in 5year-olds with prenatal polycyclic aromatic hydrocarbons (PAH) exposure rather than chlorpyrifos, thus, raising an issue of the shift in chemical exposure association with increase in age. In each of these analyses, statistical modeling showed that the exposures were independently associated with IQ, and no significant interaction was observed with the other chemical. While this is a statistically sound approach to determine independent responses, panel members noted that it is very difficult to identify the independent physiological effects of a single chemical in this type of multi-chemical exposure scenario." [any postnatal measures PAH, CPF, DZN other-hiearchal analysis, regression trees, other ways to evaluate multiple chem exp]
  - Study design did not include repeated exposure measures over time – cannot assess changes in exposures over time in relation to ND

- **2012 Federal Peer Review --** "even low levels of lead can impact neurodevelopment, and even that the observed neurobehavioral deficits are more pronounced at lower blood lead levels when compared with higher blood lead levels".
    - **Review Jan 2013 lead analyses;** external data NYC DOH; assumptions needed if CPF-Pb correlated/conF
- **2008 SAP --** "In order to eliminate the possible causes of neurodevelopmental effects by other pesticides in the Columbia study, it is suggested that EPA should repeat the pre-post residential cancellation analysis done for chlorpyrifos using other pesticide measurements, such as malathion diacid (MDA), a specific metabolite of malathion. The outcomes from those additional analyses will either confirm or reject EPA's preliminary conclusion that chlorpyrifos is likely to play a role in the neurodevelopmental outcomes."
    - **Do this –** MDA strat pre==1, post==1 – Ho: no difference
- **2008 SAP --** ""It would be useful to examine the results of a statistical analysis that includes all three AChE-inhibiting insecticides in the analysis model as dichotomous variables (above or below LOD) in combination with continuous measurements for these variables. This type of analysis would likely not change the results, but it could be helpful in illustrating threshold or dose response effects."
    - **Do this model – other Op in model cont/cat – residual conF – value?**

2) **Further analysis and information to address and, if possible, better characterize uncertainty around outcome measures on learning/memory/IQ**

- **2012 SAP**-- Alternative considerations for non-quantified samples: "little use was made of techniques to integrate non-quantified samples into the statistical test…. Various methods were reviewed by the July 2010 SAP that can be applied to either normally or lognormally distributed data that include a significant (even a majority) of non-detectable sample Specifically, the use of "probability plots" was described that can yield an estimate of the geometric mean of the distribution [GM], the geometric standard deviation [GSD], and corresponding percentiles."
    a. **Describe methods considered/Sensi performed to address <LOD – pro/con**
- **Federal Peer Review --** "There is a scatterplot showing the raw scores for overall IQ and for each of the subtests, but it is not possible to obtain the necessary information to compare the distributions of these scores with the norms for the test or with any other study sample. Ideally, the means and standard deviations

for these scores should be presented for either a non-exposed or a non-exposed combined with low exposed group and these should be compared to a moderate or high-exposed group as was done for the BSID-II in the Rauh et al., 2006 paper. Here the uncertainties stem from the assumptions that are made when regression analyses are performed. The main issue here is that outliers can greatly influence the slope of the function."

a. **Prepare alt data display, possible?**
b. Provide model diagnostics CPF-IQ, LASSO

- **Federal Peer Review--**A between group analysis using inferential statistics, as was done for the Bayley Scales of Infant Development II in the Rauh et al., 2006 paper, should be performed on each variable in both studies (i.e., the Child Behavior Checklist in Rauh et al., 2006, and the full scale IQ and subscales for the WISC-IV in the Rauh et al., 2011 study). This would be the most direct and least problematic method for determining whether exposure to chlorpyrifos resulted in significant decreases in IQ or significant increases in behavioral problems "….. no information was provided regarding the qualifications of the individuals who administered and scored the tests. "
    - **New Analysis:** ave IQ by CPF group – test significance – how compare to published analysis – pro/con
    - **Provide information as to qualifications**

3) **Further analysis to assess, if possible, whether individual cohort members had the potential for exposure to chlorpyrifos and/or other acetylcholinesterase (AChE) inhibiting pesticides (e.g., diazinon, propoxur) at levels leading to greater than 10% AChE inhibition (the level used to derive the regulatory point of departure).**

- **2012 SAP--** recommended conducting a dose reconstruction analysis—"data on the concentration of chlorpyrifos in various media (*i.e*. house dust, air and water) while market basket data exists on the concentration of chlorpyrifos on food. These data provide the main tools for developing an effective exposure assessment and a subsequent reconstruction of potential dose." The agency has begun such analysis but the current draft analysis is limited without data on the exposure information relevant to individual women such that environmental chlorpyrifos exposure can then be linked to measures of blood chlorpyrifos.
    - **See Notes**
- **2012 SAP--** recommended the agency consider issues related to multiple chemical exposure (i.e., mixtures) to chlorpyrifos and other key AChE inhibiting

pesticides identified by the Columbia University studies (diazinon, propoxur). Assumptions of co-exposure will likely be grossly overestimated without access to the raw data; such raw data may enable the agency to evaluate actual co-exposure information for individuals from air monitoring samples and blood samples.

- **See Notes**